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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KRISHNAN, GANAPATHY	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 12/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/626,138	GUTH ET AL.	
	Examiner	Art Unit	
	Ganapathy Krishnan	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

Claim14 is objected to because of the following informalities: The term therapeutic is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of heart failure, does not reasonably provide enablement for prevention of the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

(A) The breadth of the claims
(B) The state of the prior art
(C) The level of one of ordinary skill
(D) The level of predictability in the art
(E) The amount of direction provided by the inventor
(F) The existence of working examples

(G) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

Claim 1 is drawn to a method for treatment or prevention of heart failure to a person in need thereof comprising administering a pharmaceutical composition comprising cilobradine or a pharmaceutically acceptable salt thereof with a suitable pharmaceutically acceptable carrier. Claim 2 is drawn to the method of prevention of heart failure. Claim 13 is drawn to the method of claim 1 comprising administration of the composition of claim 1 in combination with other therapeutic agents for the treatment or prevention of heart failure.The scope of claims 1, 2 and 13 is seen to include the administration of the said composition to a healthy mammal, and subsequent exposure to conditions that would cause heart failure, wherein the said compounds prevent said exposure from manifesting itself in said mammal so exposed.

The state of the prior art

The examiner notes that the art cited in the rejection below mentions methods for treating heart failure associated with arrhythmia. However, there is no disclosure of potential heart failure preventive activity of compounds/compositions seen in the prior art. The prior art appears to be silent with regard to preventive procedures recognized by skilled artisans in the field.

The level of one of ordinary skill

The skilled artisan in this field is that of an MD for therapeutic administration and/or a Ph.D. skilled in the development of therapeutics.

The level of predictability in the art

The examiner acknowledges the probability and predictability that administration of the said compounds may have a reasonable expectation of success for preventing heart failure. There is not seen sufficient data to substantiate the assertion that heart failure may be prevented by the use of the compounds/compositions instantly claimed.

The amount of direction provided by the inventor

The instant specification is not seen to provide enough guidance that would allow a skilled artisan to extrapolate from the disclosure and the examples provided to enable the use of the active agents to prevent heart failure. The specification also fails to direct the skilled artisan in correlative prior art procedures which might provide the basis for an advance in treating heart failure which induces prevention of the said disease.

The existence of working examples

The working examples set forth in the instant specification are drawn to data showing the pharmacological effect of cilobradine on heart rate of rats. The skilled artisan in this field would not extrapolate the preventive efficacy of the compounds claimed or the use of the same in preventive methods from just this example provided. The disclosure does not show the prevention of heart failure. However, it is seen to show the effect of the active agent on the heart rate.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure

Indeed, in view of the information set forth, the instant disclosure is not seen to be sufficient to enable the prevention of heart failure with the compounds set forth in the

claims. A skilled artisan would not extrapolate the preventive efficacy from the results disclosed for the examples in rats, set forth in the instant specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-12 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 recites the administration of the said composition "following a single or multiple stage daily application scheme". It is not clear if the said composition is administered in a single or multiple dosages daily or if the said composition is administered following the administration of some other active agent according to the scheme recited. The claim recitation is confusing and it is not clear what is intended.

Claim 14 it is not clear what is intended by the notations ACE and ARB's. The notations should be expanded. Claim 14 also does not recite the proper Markush language, "selected from the group consisting of".

Claims that depend from rejected base claims that are unclear/indefinite are also rendered unclear/indefinite and are rejected for the same reasons.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed.

Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 3-14 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 10 and 14 of copending Application No. 10/257,481 ('481 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because:

Instant Claim 1 is drawn to a method treatment or prevention of heart failure comprising administration of a composition comprising cilobradine, with dependent claims 3-14 reciting limitations drawn to dosage, type of composition and additional cardioactive agents.

Claim 10 of the copending '481 application is drawn to a method of treating myocardial diseases accompanied by hypertrophy comprising administering a composition comprising a bradycardiac substance one of which is cilobradine. Dependent claim 14 is drawn to the method of claim 10 wherein the composition further comprises specific classes of cardioactive substances.

A patentable distinction is not seen between instant claims 1 and 3-14 and claims 10 and 14 of the copending '481 application, since heart failure is a clinical manifestation of myocardial disease accompanied by hypertrophy (see Merck Manual, 15th Edition, 1987, page 521, lines 22-25, under Prognosis). The claims of the instant application must recite limitations that are patentably distinct from those of the claims in the copending '481 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Joint Inventors

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 3-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Psiorz et al (US 5,175,157) in combination with and Rieu et al (Eur. J. Med. Chem., 1993, 28, 683-691), The Merck Manual (1987, Fifteenth Edition, pp 519-521), Bergeron (US 6083991), Hodges et al (US 5308853), Kleeman (US 5,968,978) and Liu (US 5,721,217).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 1 is drawn to a method for treatment or prevention of heart failure to a person in need thereof comprising administering a pharmaceutical composition comprising cilobradine or a pharmaceutically acceptable salt thereof with a suitable pharmaceutically acceptable carrier. Dependent claims 3-14 recite limitations drawn to the type of formulation of the composition, the dosage, combination of cilobradine with other therapeutic agents that treat ot prevent heart failure and specific therapeutic agents.

Psiorz et al teach cyclic amino derivatives of general formula (I) (col. 1, lines 35-52) and the specific compound 3-[(N-(2-(3,4-dimethoxyphenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepine-2-one, which is cilobradine (col. 35, lines 54 through col. 36, line 6) are cardioactive agents that lower heart rate (col. 36, line 52 thro col. 37, line 25). They also teach effective dosage ranges for the same and also physiologically acceptable salts and compositions comprising the active agents and other active agents, carriers, diluents in galenical preparations such as tablets, capsules, powders, suspensions, drops, ampoules, syrups or suppositories (col. 36, lines 34-51). Substance A in the table at the top of column 37 is cilobradine.

Rieu et al disclose that cilobradine, a bradycardiac agent with no negative inotropic or hypotensive activity exhibits protective effects in angina and has therapeutic potential in the treatment of chronic stable angina and heart failure (page 683, see introduction).

The Merck Manual teaches that the clinical manifestations of hypertrophic cardiomyopathy are palpitations (irregular, rapid beating of pulsation of the heart) angina, sudden death and heart failure. Palpitations are produced by ventricular or atrial arrhythmias (page 520, lines 5-13 and page 521, lines 22-25). It also gives rise to hypertension (page 522, see paragraph under Symptoms, Signs and Diagnosis).

Bergeron teaches that cardiac arrhythmia is often associated with myocardial infarction and atherosclerotic heart diseases that can lead to life threatening effects (col. 1, lines 41-48). Bergeron also teaches the use of vasodilators, angiotensin converting enzyme inhibitors and cardioglycosides in a composition for the treatment of cardiac arrhythmias (col. 6, lines 51-67).

Hodges et al teach the use of angiotensin II antagonists for the treatment of hypertension and congestive heart failure (see abstract, col. 1, lines 10-39, col. 76, lines 41-49).

Kleeman teaches the use of therapeutic agents like diuretics, cardiac glycosides, ACE inhibitors, angiotensin receptor blockers (ARB's) and beta-blockers for the treatment of heart failure (col. 11, line 58 through col. 12, line 20).

Liu teaches the use of inotropic agents for the treatment of heart failure (col. 4, lines 5-12; col. 62, line 65 through col. 67, line 20).

It is seen from the teaching of the Merck Manual, Bergeron and Hodges that arrhythmias are associated with heart failure. Since Psiorz teaches that cilobradine lowers heart rate and Rieu teaches that cilobradine has no negative inotropic or hypotensive effect, it would have been

obvious to one of ordinary skill in the art at the time the invention was made to use cilobradine in a method of treating heart failure and also use it in combination with other therapeutic agents for treating heart failure selected from a diuretic, cardioglycoside, a vasodilator, an angiotensin I converting enzyme inhibitor, ARB's, beta-blockers and inoptropes since they are known to be used for the same purpose as disclosed in the prior art.

The prior art of record teaches that cilobradine and cardioactive compounds like diuretic, cardioglycoside, a vasodilator, an angiotensin I converting enzyme inhibitor, ARB's, beta-blockers and inoptropes are known to be used in methods for treating hypertrophic myocardial diseases associated with arrhythmia including heart failure. Accordingly, it would seem to logically follow from the teaching in the prior art that the joint use to accomplish the same purpose would produce the same effect and would supplement each other. From the teachings of the prior art, it would flow logically, in the absence of proof to the contrary, that the joint use of the said compounds in methods for treating heart failure is not patentable. In re Crockett, 47 CCPA 1018, 279 F.2d 274, 126 USPQ 186 (1960); In re Heinrich, 46 CCPA 933, 268 F.2d 753, 122 USPQ 388; In re Pinten, Weissenfels, and Junger (CCPA) 173 USPQ 801; In re Kerkhoven 205 USPQ 1069.

Conclusion

Claims 1-14 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

GK